A1 concld

(c) about 0% to about 10% by weight of a binder selected from the group consisting of sodium carboxymethylcellulose, hydroxypropylmethylcellulose, potassium alginate, sodium alginate and partially pregelatinized corn starch. --

A2

-- 5. (Amended) A pharmaceutical composition comprising a core and an enteric coating for said core, said core comprising about 80% to about 100% by weight of an acid labile medicament which is 2′,3′-dideoxyinosine (ddI), about 0% to about 10% by weight of a disintegrant, and about 0% to about 10% by weight of a binder selected from the group consisting of sodium carboxymethylcellulose, hydroxypropylmethylcellulose, potassium alginate, sodium alginate and partially pregelatinized corn starch, said composition being devoid of a protective coat or subcoat between the core and the enteric coating. --

A3

-- 27. (Amended) The pharmaceutical composition of Claim 5 wherein said core comprises about 95% by weight 2′,3′-dideoxyinosine, about 1% by weight sodium carboxymethylcellulose and about 4% by weight sodium starch glycolate. --

--28. (Amended) The pharmaceutical composition of Claim 5 wherein said composition is encapsulated in a capsule for oral administration. --

REMARKS

Claims 1, 4 to 24 and 27 to 31 as present and amended are present for purposes of prosecution.

Reconsideration of the rejection of this application is respectfully requested in view of the above amendments and the following remarks.

Applicants' invention as claimed is defined as a pharmaceutical composition (Claim 5) which includes a spheronized beadlet (Claim 1) which contains from about 80 to about 100% by weight of an acid labile medicament which is 2′,3′-dideoxyinosine, and which may also include a disintegrant and/or a binder. In Claim 5, the composition is defined as including a core and an enteric coating therefor. Claim 5 has been amended to indicate that the composition is devoid of a protective coat or subcoat between the core and the enteric coating. Basis for this amendment is found in the Specification on page 9, lines 14 to 17 and in the examples.

Claims 5, 7-18, 21-24, 26, 27 and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-12 of U.S. Patent No. 6,331,316. The Examiner contends that

> "Although the conflicting claims are not identical, they are not patentability distinct from each other because, the pharmaceutical composition comprising core and coating of the instant application is obvious over the tablet comprising core and coating of USPN 6,331,316."

Enclosed herewith is a terminal disclaimer which overcomes the above rejection based on a nonstatutory double patenting ground. Also enclosed herewith are copies of recorded assignments which show that the subject application and U.S. Patent No. 6,331,316 are commonly owned, that is, by Bristol-Myers Squibb.

Claims 1, 2, 4-6, 8 and 21-23 are rejected under 35 U.S.C. §102(b) as being anticipated by Howard et al. US 5,049,394. The Examiner contends that:

> "Howard teaches high drug load pharmaceutical composition comprising from about 80% to about 96% of drug, *e.g.*, erythromycin; from about 1% to about 12% binder-plasticizer, such as, hydrophilic polymers; 0.5% to about 12% of starch-based excipient, such as, sodium starch glycolate, pregelatinized starch, or polyvinylpyrrolidone; and from about 0.2 to about 5% water-soluble binder, *e.g.*, hydroxypropylmethyl cellulose (columns 2-4). The composition is in spheronizer to form beads that may be coated with film former and plasticizer, and the coated beads can be filled into hard shell capsules (columns 4-5)."

It is submitted that Applicants' invention as now claimed is patentable over Howard et al. As indicated, Applicants' composition as now claimed defines the acid labile medicament as 2′,3′-dideoxyinosine.

Howard et al. discloses beads containing more than about 80% by weight drug which drug may be an angiotensin converting enzyme (ACE) inhibitor, as well as

> "...anti-hypertensive agents such as nifedipine and verapamil, diuretics such as hydrochlorothiazide, bendroflumethiazide or chlorthalidone, beta-blockers such as propano-lol HCl or atenolol and anti-infectives such as erythromycin, beta lactams, penicillins, other macrolides or lincosamides." (Col. 3, lines 23 to 28)

As indicated above, Applicants' claims now define the acid labile medicament as 2′,3′-dideoxyinosine. There is no disclosure or suggestion in Howard et al. of a pharmaceutical composition which includes 2′,3′-dideoxyinosine as the pharmaceutical. There is no disclosure or suggestion in Howard et al. that the Howard et al. composition could be employed to carry 2′,3′-dideoxyinosine. Accordingly, it is clear that Howard et al. does not anticipate or make obvious Applicants' composition as claimed.

Claims 1, 2, 4-21 and 25 are rejected under 35 U.S.C. §102(b) as being anticipated by Morella et al. WO 94/03160. The Examiner contends that

> "Morella teaches pelletized composition comprising core including 0.1 to 95% active ingredient, 0.1 to 55% binding agent, filler, carrier, excipients, and glidants (see

abstract, and pages 6-7). The active ingredient can be erythromycin (page 4). The core is further being coated with 3 to 50% polymer, 0 to 50% plasticizer (pages 8-9, and formulations 1-7)."

Morella et al. discloses a pelletized sustained release pharmaceutical composition which includes a core element which includes 0.1 to 95% by weight of an active ingredient which as disclosed at pages 3 and 4 includes a

> "...xanthine oxidase inhibitor, antiarrhythmic, anticoagulant, gold compound, dopamine agonist, diuretic, anticancer, skeletal muscle relaxant, antimalarial, hormone, antipsychotic, antihistamine, immunosuppressive, antileprosy, carbonic anhydrase inhibitor, antibiotic, antifungal, corticosteroid, MAO-1, vasodilator, thyroid agent, sympatholytic, H_2-antagonist, stimulant, anticoagulant, anticonvulsant, antituberculosis, hypoglycaemic, glucocorticoid or antidepressant agent.
>
> "The active ingredient of low aqueous solubility may be an NSAID or an acid or salt thereof. The NSAID ingredient in the pelletized sustained release pharmaceutical composition according to the present invention may be selected from low aqueous solubility forms of Diclofenac, Etodolac, Fenoprofen, Fluorbiprofen, Ibuprofen, Ibuproxan, Indomethacin, Ketoprofen, Ketorolac, Nabumetone, Naproxen, Phenylbutazone, Piroxicam, Priprofen, Tolmetin, Aspirin, Sulinac, Diflunisal, Indoprofen, Mefanamic Acid, Fenclozic Acid, Alclofenac, Bucloxic Acid, Meclofenamic Acid, Flufenamic Acid, Cinchophen Cinmetacin, Ibufenac, Furobufen, Prodolic Acid, Oxoproxin, Clonixin, Fluprofen, Flutiazin. The present invention is particularly applicable to NSAID's of low aqueous solubility. Diclofenac, Ketorolac and Indomethacin are preferred.
>
> "The active ingredient of low aqueous solubility may be any other suitable ingredient, for example low aqueous solubility forms of Allopurinal, Amiodarone Hydrochloride, Anisindione, Auranofin, Benzocaine, Bromocriptine Mesylate, Bumetanide, Busulfan, Chlorambucil, Chloroquine, Chlorphenesin Carbomate, Chloprothixene, Clemastine Fumarate, Dehydrocholic Acid, Dichlorphenamide, Doxycycline Monohydrate, Erythromycin, Etoposide, Griseofulvin, Haloperidol, Hydrocortisone, Levothyroxine Sodium, Liothyronine Sodium, Lovastafin, Mephenytoin, Methazolamide, Methclothiazide, Metyrosine, Nitrofarantoin, Norfloxacin, Oestropipate, Famotadine, Pemoline, Phenacemide, Pimozide, Quinethazone, Rifampin, Sulfisoxazole, Tamoxifen Citrate, Tetracycline, Tolazamide, Triamcinolone, Trichlormethiaside, Trimethoprim, Trimipramine Maleate, Uracil Mustard and acids or salts thereof."

There is no disclosure or suggestion in Morella et al. of using 2′,3′-dideoxyinosine in their pellets. Accordingly, it is clear that Applicants' compositions as now claimed, which define the acid labile medicament as 2′,3′-dideoxyinosine, are neither anticipated or made obvious by Morella et al.

Claims 1, 2, 4-25 are rejected under 35 U.S.C. §103(a) as being unpatentable over Howard et al., in view of Morella et al., and Sachs et al. US 6,274,173. The Examiner contends that

"Howard and Morella are relied upon for the reasons stated above. The references are silent as to the teaching of alkaline binder as claimed in claims 23 and 24.

"Sachs teaches pharmaceutical composition comprising acid labile active agent, binder, filler, and coating includes plasticizer (columns 3-4). The composition further comprising disintegrants, and lubricants (columns 5-6). Thus, it would have been prima facie obvious for one of ordinary skill in the art to modify the composition of Howard and Morella using carboxymethyl cellulose in view of the teaching of Sachs, because the references teach the advantageous results in the use of binder and disintegrant in pelletize or beads. The expected result would high dosage acid labile drug in pellet form useful in pharmaceutical art."

It is submitted that Applicants' invention as claimed is patentable over a combination of Howard et al. taken in view of Morella et al. and Sachs et al.

Howard et al. and Morella et al. disclose compositions which include a drug which is other than 2′,3′-dideoxyinosine as now claimed. There is no disclosure or suggestion in either of these references of a 2′,3′-dideoxyinosine composition containing drug loads of at least 80%.

U.S. Patent No. 6,274,173 to Sachs et al. discloses an oral pharmaceutical composition which includes an acid-labile irreversible proton pump inhibitor such as pantoprazole, as well as omeprazole or lansoprazole. The composition is used in conjunction with an antimicrobially-active ingredient on Helicobacter.

Examples of suitable antimicrobially-active ingredients disclosed by Sachs et al. (active against Helicobacter and, in particular, against Helicobacter pylori)

"are enumerated in European Patent Application EP-A-0282131. These active ingredients include, for example, bismuth salts (such as bismuth subcitrate or bismuth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitrofurantoin or furazolidone), metronidazole, tinidazole, nimorazole or antibiotics. Examples of antibiotics which may be mentioned in this connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin; macrolides, such as erythomycin, azithromycin, clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin; tetracyclines, such as tetracycline, chlorotetracycline, oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxim proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin, or other different antibiotics, such as chloramphenicol.

"Particularly worth of mention in this connection is also the conjoint administration of pantoprazole with a plurality of antimicrobially-active ingredients, for example with a

combination of bismuth salt and/or tetracycline with metronidazole, or with the combination of amoxicillin or clarithromycin with metronidazole.

"Antimicrobially-active ingredients which may be emphasized are erythromycin, azithromycin, clarithromycin, clindamycin, rifampicin, ampicillin, mezlocillin, amoxicillin, tetracycline, minocycline, doxycycline, imipenem, meropenem, cefalexin, cefuroxime axetil, cefpodoxime proxetil, cefaclor, cefadroxil, ciprofloxacin, norfloxacin, ofloxacin and pefloxacin.

"Clarithromycin and amoxicillin may be mentioned as antimicrobially-active ingredients which should be particularly emphasized."

There is no disclosure or suggestion in Sachs et al. of a pharmaceutical composition which includes 2′,3′-dideoxyinosine. Accordingly, Sachs et al. is no more relevant to Applicants' invention as now claimed than is Howard et al. and Morella et al. None of these references taken alone or in combination discloses or suggests a pharmaceutical composition which contains high drug loads of 2′,3′-dideoxyinosine, that is, at least 80% by weight. None of these references taken alone or in combination discloses or suggests Applicants' inventive concept of a 2′,3′-dideoxyinosine formulation containing a 2′,3′-dideoxyinosine load of at least 80% by weight. Accordingly, none of the cited references adds to anything to the other cited references which would make Applicants' compositions obvious. For the above reasons, it is submitted that Claims 1, 2, 4 to 25 are patentable over Howard et al. taken in view of Morella et al. and Sachs et al.

Claims 3 and 26-31 are rejected under 35 U.S.C. §103(a) as being unpatentable over Morella et al., in view of Howard, and Bogardus et al. US 6,207,650. The Examiner contends that

"Howard and Morella are relied upon for the reasons stated above. The references are silent as to the teaching of the specific active agent as claimed in claims 3, and 26.

"Bogardus teaches pharmaceutical composition comprising antiviral drug, *e.g.*, 2′,3′-dideoxyinosine in the form of powders, granules that can be enteric coated (columns 4-5). Accordingly, it would have been prima facie obvious for one of ordinary skill in the art to prepare the composition of Morella and Howard using 2′,3′-dideoxyinosine as active ingredient in view of the teaching of Bogardus because the references teach the advantageous result of acid labile drug in oral dosage form."

It is submitted that Applicants' invention as claimed is patentable over each of the above-cited references taken alone or in combination.

As previously indicated, Morella et al. and Howard et al. disclose formulations which may be employed for various drugs none of which includes 2′,3′-dideoxyinosine. These references do not disclose or suggest Applicants' inventive concept of a composition containing at least 80% by weight 2′,3′-dideoxyinosine.

Accordingly, it is submitted that Applicants' invention as claimed is patentable over each of Morella et al. and Howard et al.

U.S. Patent No. 6,207,650 to Bogardus et al. discloses 2′,3′-dideoxyinosine and pharmaceutical compositions containing 2′,3′-dideoxyinosine which include tablets, capsules, powders, granules, which may be enteric coated and buffered. However, there is no disclosure or suggestion of a composition containing at least 80% by weight 2′,3′-dideoxyinosine. This is Applicants' inventive concept and it is neither disclosed nor suggested in Bogardus et al. Accordingly, it is clear that Applicants' invention as claimed is patentable over Bogardus et al.

It is also submitted that Applicants' invention as claimed is patentable over a combination of Morella et al., taken in view of Howard et al. and Bogardus et al. Morella et al. and Howard et al. disclose hundreds, if not thousands, of possible drugs, none of which includes 2′,3′-dideoxyinosine. Bogardus et al. disclose formulations containing 2′,3′-dideoxyinosine but does not disclose or suggest formulations containing at least 80% by weight 2′,3′-dideoxyinosine. There is nothing in the teachings of Morella et al. and Howard et al. which would suggest to one skilled in the art that the Morella et al. and Howard et al. formulations could include 2′,3′-dideoxyinosine. All drug compounding techniques do not apply to all drugs. Bogardus et al. do not make the slightest hint or suggestion as to how to compound 2′,3′-dideoxyinosine into a formulation containing at least 80% by weight 2′,3′-dideoxyinosine. There is nothing in any of the cited references which suggests or makes the slightest hint that 2′,3′-dideoxyinosine could be compounded into a formulation containing at least 80% by weight 2′,3′-dideoxyinosine. Accordingly, it is submitted that the cited combination of references do <u>not</u> make Applicants' composition as claimed obvious.

A determination of obviousness under 35 U.S.C. §103 is a legal conclusion based upon factual evidence. The factual inquiries on which the conclusion is based are those defined in Graham v. John Deere Co., 383 U.S. 1 (1966), and restated in Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81 (Fed. Cir. 1986), cert. den., 107 S. Ct. 1606 (1987). These factual inquiries are:

(1) determining the scope and content of the prior art;

(2) ascertaining the differences between the invention and the prior art and the claims at issue, and

(3) resolving the level of ordinary skill in the pertinent art.

Obviousness is tested by what the combined teachings of the prior art references would have suggested to those of ordinary skill in the art, not by whether it might have been "obvious to try" a particular combination of elements from the prior art (In re Fine, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988), In re Wiggins, 158 U.S.P.Q. 199 (1968); In re Mercier, 185 U.S.P.Q. 774 (1976); In re Yates, 211 U.S.P.Q. 1149 (1981)). The teachings of the prior art can only be combined if there is some suggestion or incentive in the prior art to do so (ACS Hospital Systems, Inc. v. Montefiore Hosp. et al., 221 U.S.P.Q. 929 (CAFC 1984)).

Further, as stated in W.L. Gore & Assoc., Inc. v. Garlock, Inc., 220 U.S.P.Q. 303 (Fed. Cir. 1984):

> "To imbue one of ordinary skill in the art with knowledge of the invention..., when no prior art reference or references... convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."

Applying the above law, it will be seen that Applicants' invention as claimed is patentable over the cited references each taken alone or in combination.

In applying the criteria for patentability as enunciated in Graham v. John Deere Co., supra, it is seen that:

(1) the scope of the content of the prior art has been reviewed above.

(2) the differences between the invention and the prior art have been set out, namely, that the prior art does not disclose or suggest a composition containing high drug loads of 2′,3′-dideoxyinosine.

(3) the level of ordinary skill in the art is exceedingly high and involves scientists having Masters, Ph.D and M.D. degrees.

It is submitted that there is no disclosure or suggestion in any of the cited references or combination thereof of the claimed composition. Accordingly, absent the use of hindsight in view of Applicants' disclosure, there would be no reason for one skilled in the art reading the cited references, to combine these references. The use of hindsight in view of Applicants' disclosure in combining references to reject Applicants' claims is clearly improper in view of In re Pye et al., 148 U.S.P.Q. 426 (CCPA 1966); ACS Hospital Systems, Inc. v. Montefiore Hospital, supra; and W.L. Gore & Assoc., Inc. v. Garlock, Inc., supra.

The Examiner has not established any factual basis sufficient to support the Examiner's conclusions and thus establish a prima facie case for obviousness of Applicants' invention as claimed. In re Piasecki, 745 F.2d 1468, 223 U.S.P.Q. 785 (Fed. Cir. 1984). In essence, the Examiner has merely alleged that the differences between Applicants' invention and the cited art are obvious, but has not set forth any basis in logic or scientific principle to support such contention as required under In re Soli, 317 F.2d 941, 127 U.S.P.Q. 797 (CCPA 1963). The very combination of references is improper as being based on hindsight in view of Applicants' disclosure.

The Examiner indicates that

> "the prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Yajima et al., Erkoboni et al., Koszalka et al., and Mitsuya et al. are cited as being of interest for the teaching of acid labile drug."

It is submitted Applicants' invention as claimed is patentable over each of the above references taken alone or in combination or combination with the previously discussed cited references.

The Yajima et al. and Erkoboni et al. patents do not disclose or suggest formulations containing 2′,3′-dideoxyinosine and thus are no more relevant than Morella et al. and Howard et al. discussed above.

U.S. Patent No. 4,920,210 to Koszalka et al. discloses 2′,3′-dideoxynucleosides; 2′,3′-dideoxyinosine is not specifically disclosed. Koszalka et al. disclose formulations which may be enteric coated. Various tablet and capsule formulations are disclosed in Examples 1 and 2, none of which includes an active ingredient in an amount of at least about 80% by weight. Thus, Koszalka et al. is even less relevant than the cited Bogardus et al. discussed hereinbefore.

U.S. Patent No. 5,254,539 to Mitsuya et al. disclose a method for treating HIV with 2′,3′-dideoxyinosine. However, there is no disclosure or suggestion of a formulation containing at least 80% by weight 2′,3′-dideoxyinosine. Accordingly, Mitsuya et al. is no more relevant than Bogardus et al. discussed hereinbefore.

The combination of the above references taken together with the previously discussed references do not disclose or suggest Applicants' 2′,3′-dideoxyinosine composition as claimed for the reasons set out above. None of these references alone or in combination discloses or suggests Applicants' invention as claimed.

In view of the foregoing, it is believed that Claims 1, 4 to 24 and 27 to 31 are in condition for allowance.

Respectfully submitted,

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Date: Oct. 22, 2002

MARKED UP VERSION TO SHOW CHANGES

-- 1. (Amended) A spheronized beadlet comprising:

(a) about 80% to about 100% by weight of an acid labile medicament which is 2',3'-dideoxyinosine (ddI);

(b) about 0% to about 10% by weight of a disintegrant; and

(c) about 0% to about 10% by weight of a binder selected from the group consisting of sodium carboxymethylcellulose, hydroxypropylmethylcellulose, potassium alginate, sodium alginate and partially pregelatinized corn starch. --

-- 5. (Amended) A pharmaceutical composition comprising a core and an enteric coating for said core, said core comprising about 80% to about 100% by weight of an acid labile medicament which is 2',3'-dideoxyinosine, about 0% to about 10% by weight of a disintegrant, and about 0% to about 10% by weight of a binder selected from the group consisting of sodium carboxymethylcellulose, hydroxypropylmethylcellulose, potassium alginate, sodium alginate and partially pregelatinized corn starch, said composition being devoid of a protective coat or subcoat between the core and the enteric coating. --

-- 27. (Amended) The pharmaceutical composition of Claim [26] 5 wherein said core comprises about 95% by weight 2',3'-dideoxyinosine, about 1% by weight sodium carboxymethylcellulose and about 4% by weight sodium starch glycolate. --

-- 28. (Amended) The pharmaceutical composition of Claim [26] 5 wherein said composition is encapsulated in a capsule for oral administration. --